REMARKS

Claims 1-31 and 33-49 are pending. Claims 1-31 and 33-49 are being examined as part of the invention of Group I and upon the elected species which is the peptide SEQ ID NO: 1 wherein the disease is assessed by scintigraphy.

Restriction Requirement

In their December 1, 2005 Response, applicants elected, with traverse, Group I, claims 1-31 and 33-49, drawn to a product, methods of making the product, and uses of a product wherein the metal surface is selected from the group consisting of gold, silver and copper; the complex forming metals are selected from the group consisting of transition, lanthanide and actinide metals; the targeting moiety is a peptide; and the disease is an oncological disease.

Applicants further elected, with traverse, the species wherein the peptide is SEQ ID NO: 1, and wherein the disease is assessed by scintigraphy. Claims 1-31, 33 and 35-49 read on the elected species.

In the present Office Action, the Examiner has stated that applicant's argument in the December 1, 2005 Response regarding the restriction requirement is not persuasive. The Examiner alleges that the groups of invention lack unity because they do not contain a metal support which defines a contribution over the prior art and that SEQ ID NO: 1 does not define a contribution over the prior art. The Examiner references the current §103 rejection as support for this position. The Examiner further alleges that the targeting moiety and ligand combinations which are conjugated to the metal support result in a vast number of complexes and that the diseases for which the complexes may be used vary extensively.

Applicants respectfully point out that the Examiner again makes statements about whether certain aspects of the invention define a contribution over the prior art. Applicants

respectfully maintain that this is improper, particularly where, as here, no art has been cited which discloses the claimed features. In particular, it should be noted that no art has been cited disclosing:

1. The claimed metal support surface and
2. A conjugate which is releasably bound to the support surface and is released from said surface upon coordination with the metal ion.

35 U.S.C. § 103(a) Rejection

Claims 1-31 and 33-49 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,921,526 ("Hoffman"). Applicants respectfully disagree.

Initially, applicants point out that in order to establish a *prima facie* case of obviousness, three basic criteria must first be met: (1) there must be some suggestion or motivation in the cited references to modify the reference or to combine reference teachings to obtain Applicant's claimed invention; (2) there must be a reasonable expectation of success; and (3) the cited references must teach or suggest all of the claimed limitations. MPEP § 2143.

Because (a) Hoffman fails to teach all of the claimed limitations, and (b) there is no motivation to modify Hoffman to achieve the claimed invention and (c) there is no reasonable expectation of success, applicant respectfully submits that there is not a *prima facie* case of obviousness.

Hoffman Fails to Teach or Suggest All of the Claim Limitations

Applicants respectfully disagree because Hoffman fails to teach or suggest all of the claimed limitations. Applicants point out that, in order to find obviousness, all of the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 474, 496 (CCPA 1970); MPEP 2143.03.

Independent claim 1 reads:

> A composition for generating a complex-forming metal ion labeled agent, the compositions comprising:
>
> (a) a metal support surface; and
>
> (b) a conjugate releasably bound to the support surface, the conjugate comprising a ligand and a targeting molecule;
>
> wherein the conjugate coordinates with a complex-forming metal ion so that the labeled conjugate is released from the support surface.

Applicants respectfully maintain that the Examiner has not identified where the Hoffman reference discloses or suggests the limitations:

(a) The claimed metal support surface and
(b) A conjugate which is releasably bound to the support surface and is released from said surface upon coordination with the metal ion.

Applicants respectfully point out that the instant invention provides compositions for labeling a conjugate with a detectable metal ion and simultaneously separating the labeled conjugates from the unlabeled ones as well of methods of accomplishing such labeling. Specifically, the instant claims require a metal support surface and a conjugate (comprising a ligand and a targeting molecule) which is bound to the metal support surface, but will be released therefrom upon coordination with a detectable metal ion. Thus, the metal ion labeled ligand is released from the metal support and the unlabeled conjugates remain bound. The specification explains that in a preferred embodiment:

> The invention includes a method of producing metal labeled imaging and radiopharmaceutical agent formulations having high specific activity. The invention includes labeling peptides…or other organic molecules that are attached toa support surface, preferably gold, via a group or a molecule that binds the surface. The surface binding molecule is preferably the sulfur group of a cysteine (this cysteine will ultimately be a part of the metal chelate). During the labeling of the peptide with a metal, (which is preferably a radioisotope, such as 99m Tc), the complexation of the metal to the chelator, and hence to the sulfur of the cysteine, causes weakening of the gold-cysteine bond with the result that the metal complexed peptide

> leaves the surface and moves into solution. Uncomplexed peptides remain attached to the gold surface. The result of this selective cleavage from the surface is that the radiolabled peptide is produced without added carrier giving a high specific activity formulation.

WO 00/48639, p. 3 lines 19-31.

The Examiner contends that Hoffman discloses a metal complex comprising SEQ ID NO: 1, having a metal, chelator, linker and targeting moiety (SEQ ID NO: 1) where the complexes may be used as a therapeutic and imaging agent for cancer cells.

Applicants submit that Hoffman does not disclose or suggest either of these claimed elements. Instead, Hoffman is directed to compounds for use as radiopharmaceuticals which include a group capable of complexing a metal (e.g. a metal chelator), a moiety capable of binding to a gastrin releasing peptide receptor and optionally a spacer or linker group. See e.g. Col 4 – 5. Furthermore, Hofffman does not teach use of a metal support to label these compounds. In fact, Hoffman does not even teach use of conjugates which may be bound to a metal support but are realeased upon complexation with a metal ion. Indeed, the labeling methods and compositions taught by Hoffman all require dissolution in a solution, with no teaching or suggestion of a solid, metal support. For example, Hoffman teaches:

> When the metal is technetium-99m, the following general procedure can be used to form a technetium complex. A peptide-chelator conjugate **solution** is formed by initially **dissolving** the conjugate in aqueous alcohol such as ethanol. The **solution** is then degassed to remove oxygen. When an –SH group is present in the peptide, the thiol protecting groups are removed with a suitable reagent, for example, sodium hydroxide, and are then neutralized with an organic acid such as acetic acid (pH 6.0-6.5). In the labeling step, sodium pertechnetate obtained from a molybdenum generator is added to a **solution** of the conjugate with a sufficient amount of a reducing agent, such as stannous chloride, to reduce technetium and is then heated.

Col 8, line 61- Col. 9, line 4. See also, Col. 9, lines 10-19 ("In an alternative method, the labeling can be accomplished by a transchelation reaction. The technetium source is a solution of technetium complexed with labile ligands facilitating ligand exchange with the selected

chelator. Examples of suitable ligands for transchelation include tartrate, citrate, gluconate, and heptagluconate. It will be appreciated that the conjugate can be labeled using the techniques described above, or alternatively, the chelator itself may be labeled and subsequently coupled to the peptide to form the conjugate: a process referred to as the 'prelabeled chelate" method.")

No Motivation to Modify Hoffman or Reasonable Expectation of Success

Applicants further disagree because there is no motivation to modify Hoffman to create the claimed invention. As stated by the Court in *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783-1784 (Fed. Cir. 1992): "the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Applicants maintain that the reference relied upon by the Examiner fails to provide the necessary incentive or motivation which would produce the invention as claimed.

For example, the problem solved by the claimed invention - simple separation of labeled and unlabeled ligand - is not mentioned, let alone solved by the Hoffman patent. Indeed, Hoffman only teaches how to remove certain labeled contaminants:

> The labeled conjugate can be separated from the contaminants 99m Tc O4- and colloidal 99mTcO2 chromatographically, for example with a C-18 Sep Pak cartridge…

Col 9, lines 5-8.

Not only must there be a motivation to combine the asserted reference, but there must also be a reasonable expectation of success. MPEP § 2143.02. However, for the same reason that there is no motivation to modify Hoffman, there is also no reasonable expectation of success. That is, one of ordinary skill in the art would not expect success in modifying Hoffman to separate labeled and unlabeled ligand because Hoffman fails to identify the problem of

removing unlabeled ligand or to suggest the claimed solution. Hoffman instead shows how to remove certain labeled contaminants.

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In view of the remarks and comments herein, pending claims 1-31 and 33-49 in the present application are believed to be in condition for allowance, early notice of which is earnestly sought. If there are any reasons why such a Notice would not issue, the Examiner is respectfully requested to contact the Applicants' undersigned counsel for an interview.

No additional fees are believed due. However, the Director is hereby authorized to charge any deficiencies and credit any overpayments to Deposit Account No. 50-0540.

Respectfully submitted,

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/Henry J. Cittone/

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